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| 10/520,084 | 05/06/2005 | Ajit Lalvani | GRT/3772-22 | 9379 |

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| EXAMINER | |
|---|---|
| GRASER, JENNIFER E | |
| **ART UNIT** | **PAPER NUMBER** |
| 1645 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/520,084 | LALVANI ET AL. | |
| | Examiner | Art Unit | |
| | Jennifer E. Graser | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 August 2008*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *96-115* is/are pending in the application.

4a) Of the above claim(s) *102-105 and 112-115* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *96-101 and 106-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted on 8/25/08 is made. Claims 96-115 are currently pending. Claims 102-105 and 112-115 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 96-101 and 106-111 are currently under examination.

### *Election/Restrictions*

1. Newly submitted claims 102-105 and 112-115 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The claims drawn to kits were restricted from the original claims (drawn to methods) in the Restriction Requirement mailed 10/2/07. The kit claims were withdrawn from consideration in the non-final Office Action mailed on 3/25/08. The newly presented kit claims set forth in new claims 102-105 and 112-115 have been placed in Group IV as is outlined in the Restriction Requirement mailed 10/2/07.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 102-105 and 112-115 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

With respect to Applicant's request for rejoinder pending allowance of the elected methods claims, the instant claims are drawn to methods not 'a product'. The product,

ESAT-6 protein or its peptide epitopes, has not been examined. A method for diagnosing M.tuberculosis is what has been examined. MPEP 821.04(b) is a requirement for rejoinder of a process requiring an allowable product and would not apply to the instant situation. The instant examination was not drawn to the allowability of the ESAT-6 protein or its epitopes. This would require a separate examination.

### *Claim Rejections - 35 USC § 112-2nd paragraph*

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 96-101 and 106-111 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 96 and 102 are vague and indefinite because there is no correlation between the 'frequency' of antigen-responsive T cells which is determined in line 3 of part (b) and the positive or negative response. What frequency indicates a positive response and what frequency indicates a negative response? There is often a frequency detected even when it is not considered a 'positive' response per se, so just determining a 'frequency' does not represent a complete and functional assay. Clarification and/or correction is required.

Claims 96 and 106 are vague and indefinite because step c) recites evaluating whether there was a 'positive response'; and then states "wherein a positive response using whole ESAT-6 or an analog thereof and a negative response using peptide epitopes or analogs thereof indicate that the individual has been recently exposed to

M.tuberculosis". It appears that both a positive response to whole ESAT-6 and a negative response to ESAT-6 peptide epitopes are needed to make the diagnosis for recent exposure to M.tuberculosis (this is what is taught in the instant specification as well). The claim as written, by merely evaluating a positive response in each separate assay, (line 1 or part c), does not reflect a working assay for detection of recent exposure to M.tuberculosis. Correction is requested.

Claims 96 and 106 are vague and indefinite due to the phrase "in each separate assay". Is this in reference to ELISPOT being performed on different aliquots? Are these the 'separate assays' which are being referenced?

Claims 99 and 109 are vague and indefinite due to the phrase "all possible peptide epitopes derived from ESAT-6". What does 'possible' mean? Is this all 5-mer sequences or something else? The metes and bounds of the phrase cannot be understood.

***Claim Rejections - 35 USC § 112- Enablement***

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 96-101 and 106-111 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification teaches a tuberculosis diagnostic test which can detect the difference from those recently exposed versus those with long-term infection. It was known in the prior art that following exposure to *M.tuberculosis* individuals have an approximately 10% risk of progressing to active tuberculosis with disease symptoms within one to two years. If the active tuberculosis does not manifest within the first 1-2 years then the residual risk of progress to active tuberculosis is 5% over the remaining lifetime of the individual. (specification page 1). *M.tuberculosis* diagnostic tests were known in the prior art to have unique problems as due to the use of BCG (closely related to M.tuberculosis) as a vaccine against tuberculosis individuals who have been vaccinated with BCG can react positively to the tuberculin skin test. Additionally, culturing of mycobacterium can take up to 8 weeks so identification tests are not always practical and obtaining the samples is often done through invasive procedures. See Lalvani et al. WO00/26248. The invention seeks to overcome the problems of the prior art and have the ability to detect those recently exposed from those with long-term infection. Working examples show the use of ELISPOT for the detection of *M.tuberculosis* exposure. The specification has found that T cells from individuals recently exposed to *M.tuberculosis* react to whole proteins from the pathogen but do not react to, or show substantially less reaction, to peptide epitopes from the pathogens. It is believed T cells appear in the later course of infection and are more mature and focused and would not be present in individual recently exposed to M.tuberculosis (specification, page 2). Additionally, the method requires knowledge or a protein and specific epitopes which are unique to the agent being tested. For instance, given the

similiarity of BCG to M.tuberculosis those exposed to BCG often test positive for tuberculosis exposure. However, BCG does not have the ESAT-6 gene and therefore can distinguish between patients with tuberculosis and patients who have been vaccinated with BCG. See WO 00/26248 paragraph bridging pages 1-2. This is vastly important. *However,* the instantly claimed method fails to require evaluating whether there was **both** a positive response to whole ESAT-6 **and** a negative response to ESAT-6 peptide epitopes. This is needed to make the diagnosis for recent exposure to M.tuberculosis. The claim as written merely evaluate a positive response in each separate assay, (line 1 or part c), and this does not reflect a working assay for detecting recent exposure to M.tuberculosis and is not enabled.

The specification is enabled for diagnosing recent exposure to *M.tuberculosis* in a host wherein the peptide epitopes are one of SEQ ID NOs: 1-17 and the protein is ESAT-6, but not for analogs of the epitopes or analogs of the ESAT-6 protein. The breadth of the instant claims are drawn to a method using polypeptides which are not specified in the sequence disclosure or even mentioned in descriptive terms, e.g., name, molecular weight, etc.. "Analogs" as encompassed in the instant claims include substitutions, additions, or deletions to be made to the defined sequences; however, the specification provides no guidance as to what amino acids may be changed without causing a detrimental effect to the protein or peptide to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made

with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. Selective point mutation to one key antigen could eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection/function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of function. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Thus, proteins of different levels of homology may not induce antibody which is recognized by the native protein. Applicants have provide no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different nucleotide substitutions and the nature and extent of the changes that can be made. It is expensive and time consuming to make amino acid substitutions at more than one position, in a particular region of the protein, in view of the many fold possibilities for change in structure and the uncertainty as to what utility will be possessed. See Mikayama et al. (Nov.1993. Proc.Natl.Acad.Sci. USA, vol. 90 : 10056-10060) which teaches that the three-dimensional structure of

molecules is important for their biological function and even a dingle amino acid difference may account for markedly different biological activities. The prior art further teaches that amino acids owe their 'significance' to their inclusion in a pattern which is directly involved in recognition by, and binding to, the receptor and the significance of the particular amino acids and sequences for different amino acids cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study. Most importantly, the specification fails to identify what is encompassed by the term 'analog' (of the protein or peptide epitope).

Given the lack of guidance contained in the specification, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

*Response to Applicants' Arguments:*

Applicants argue that since the analogs are required to be induced to a response by the same T cells that the structure would be related to the structure of the whole ESAT-6 or peptide epitope recognized by the T cell's receptor and, thus, structure and function are shared. They also argue that algorithms were known in the art that could be used to identify the analogs. These arguments have been fully and carefully considered but are not deemed persuasive. "Analogs" as encompassed in the instant claims include substitutions, additions, or deletions to be made to the defined sequences; however, the specification provides no guidance as to what amino acids may be changed without causing a detrimental effect to the protein or peptide to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are

possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. Selective point mutation to one key antigen could eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection/function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of function. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

***Claim Rejections - 35 USC § 112-Written Description***

6. Claims 96-101 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no teaching in the instant specification of the structure of an analog to the ESAT-6 protein or an analog to epitopes derived from the ESAT-6 protein. There is no teaching of which amino acids can be changed and still retain activity. The specification does not disclose any analog amino acid sequences with the function of ESAT-6. A representative number of analogs are not disclosed. There are no sequences of analogs to either the full-length ESAT-6 protein or its epitopes discloser. There is no art-recognized correlation, e.g., conserved amino acid sequence, and ability to detect recent exposure of M.tuberculosis. There is some general teaching in the art that some amino acid variations are tolerated without losing a protein's tertiary structure, but conservation of structure in not necessarily a surrogate for conservation of function. While one of skill in the art could, with the aid of a computer as suggested, could identify some homologous polypeptides, this would not tell one the structure of the polypeptides which have the same activity. Accordingly, it does not appear applicants were in possession of the claimed sequences at the time of filing.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

With the exception of ESAT-6 and its epitopes thereof, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The product itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Furthermore, In The Reagents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise

definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore the full breadth of the claims which includes analogs does not meet the written description provisions of 35 USC 112, first paragraph.

***Closest prior art, not relied on:***

a) Lalvani et al (WO 00/26248).

Lalvani et al disclose a method of diagnosing in host infection by exposure to a mycobacterium which expresses ESAT-6 comprising contacting a population of T cells from the host with one or more peptides or analogs. The peptide recited in SEQ ID NO: 1 is specifically disclosed. Lalvani et al do acknowledge on page 24, lines 2-10, that in tuberculosis-endemic countries, where a significant proportion of healthy individuals are latently infected with M.tuberculosis, the specificity of an assay based on the detection of a M.tuberculosis-sensitized cellular immune system might be lower than in their study. They also acknowledge that the assay has not been validated in children, where tuberculosis is usually a primary infection and presents acutely. In Example 6 the method does compare the use of whole ESAT-6 for detection of T cell responses versus peptides from ESAT-6. They found that peptides are able to elicit a response from both CD4 and CD8 T cells and more patients could be detected using peptides than the whole protein. See page 25 Example 6. This is the opposite of what is being detected

in the instantly claimed methods, e.g., detecting the *protein* to a greater extent than the peptides to diagnose recent exposure. Lalvani et al do not teach diagnosing in an individual 'recent exposure to the agent', nor does it teach or suggest whether the individual can recognize a protein of at least 30 amino acids (ESAT-6) to a greater extent than one or more peptide agents as is required by the instant claims.

b) Andersen et al (US Patent No. 5,955,077).

Andersen et al teach that ongoing or previous M.tuberculosis infection may be detected by using ESAT-6 polypeptides (see column 14, lines 35-65); however they do not teach or suggest a method which involves determining whether an individual has been recently exposed to the pathogen by having the ability to recognize ESAT-6 protein to a greater extent than a peptide epitope from ESAT-6.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 8:00 AM-6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached on (571) 272-0956.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645

12/4/08